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Original Scientific Paper

THROMBOTIC RISK EVALUATION OF TWO METHYLENETETRAHYDROFOLATE REDUCTASE MUTATIONS C677t AND A1298c IN VENOUS THROMBOEMBOLISM

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SUMMARY – The MTHFR mutations C677T and A1298C combined with folate and vitamin B12 deficiency lead to hypercoagulability. We evaluated thrombotic risk due to MTHFR mutations, individually and in combination, in patients with venous thromboembolism (VTE). The case-control study included groups of 262 VTE patients and 101 healthy controls. Allelic distribution of MTHFR C677T/A1298C mutations was determined by real-time polymerase chain reaction and results were statistically analyzed using χ^2-test and comparison of proportions with 95% confidence intervals (95% CI) and p=0.05. There was no statistically significant difference in the frequencies of C677T MTHFR genotypes between the patient group and controls (p=0.676; odds ratio (OR)=1.297; 95% CI 0.649-2.592), or for A1298C mutation (p=0.872; OR=0.894; 95% CI 0.564-1.419). The allele distribution of both MTHFR mutations did not show any significant differences (C677T p=0.808; OR=1.043; 95% CI 0.741-1.468 and A1298C p=0.738; OR=0.943; 95% CI 0.667-1.332). MTHFR genotype distributions did not show any significant difference between genders when analyzed with χ^2-test. When evaluating a combination of mutations, the greatest difference between the cases and controls was found in the frequencies of MTHFR TT/AA carriers (2.6%), which, however, did not reach significance (p=0.520). In conclusion, MTHFR C677T and A1298C mutations do not represent risk factors for VTE development in the group of Croatian patients.

Key words: *MTHFR (methylenetetrahydrofolate reductase); Venous thromboembolism; Genotype; Alleles*

Introduction

Methylenetetrahydrofolate reductase (MTHFR) is a key regulatory enzyme in the metabolism of folate and allows removal of homocysteine (Hcy), a

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potentially toxic amino acid[1]. An adequate supply of B vitamins to the cells is necessary for proper functioning of Hcy metabolism. Methylated form of folate is a methyl group donor and a substrate of the methionine synthesis of the remethylation pathway, which is carried out with the help of cofactors riboflavin and vitamin B12.

The metabolic disorder may be due to genetic changes in one of the enzymes involved in Hcy metabolism or nutritional deficiency of the vitamins[1]. Hyperhomocysteinemia is associated with several processes and changes at the cellular level, which has an impact on the pathophysiology of vascular disease, oxidative stress in particular[2]. It can be one of the causes of atherosclerosis, heart attack, peripheral arterial diseases, venous thromboembolism (VTE) such as deep vein thrombosis (DVT), and pulmonary embolism (PE)[3].

Point mutations of the MTHFR gene at nucleotide positions C677T (rs1801133) and A1298C (rs1801131) cause thermal lability and reduce enzyme activity by about 50%, and consequently the ability to bind folate[4]. Homozygous carriers of these mutations may have elevated plasma Hcy, which in addition to folate and vitamin B deficiency is a risk factor for the development of thrombosis[4,5]. The effect of the A1298C mutation at the Hcy level is weaker compared to the C677T[6]. However, MTHFR as a thrombotic risk factor is not exclusively a genetic factor but is considered as a mixed factor. Dietary addition of vitamins B6, B12 and folic acid can significantly diminish its impact on the development of thromboembolism[2,7-9] The prevalence of these MTHFR mutations in a particular population varies according to race and geographical area. The prevalence of MTHFR 677TT homozygotes in Europe ranges from 10% to 12% in Spain, France, Hungary, and northern Italy, while it is significantly lower in Finland and The Netherlands (4%-6%). The exception is southern Italy, especially the Campania region, where the prevalence of the TT genotype is 26% and in Sicily 20%[10]. Population frequencies of the MTHFR A1298C allele have so far been less investigated. In Canada, there are 10% of CC homozygotes, in The Netherlands approximately 9%[11], and in the Iranian population just 4%[12]. The A1298C gene polymorphism for MTHFR is associated with arterial and venous thrombosis, as well as with the risk of miscarriage and fetal loss, especially if present along with folate deficiency[9].

Among cardiovascular diseases (CVD), VTE is ranked the third most common in the world, after coronary heart disease and ischemic stroke. VTE includes two specific clinical manifestations, i.e., DVT and PE. The etiology of VTE is multicausal. Risk factors associated with the disease can be both genetic and acquired[13]. In most cases, an inherited predisposition to VTE remains clinically silent until the intervention of an additional environmental factor such as advanced age, surgery, prolonged immobilization, malignancy, oral contraceptives, pregnancy, hormone replacement therapy, long-distance travel, etc.[14-16]. Although most studies did not confirm MTHFR mutations as risk factors for VTE, the contribution of these MTHFR mutations to the thrombotic risk is still being investigated[17]. For example, the TT genotype of C677T mutation has been verified as an independent VTE risk factor in the Italian population[18].

The present study aimed to assess whether C677T and A1298C MTHFR mutations represented risk factors for the development of VTE in a selected sample of Croatian VTE patients.

Material and Methods

The case-control study was conducted in the Department of Molecular Diagnostics, Croatian Institute of Transfusion Medicine (CITM), from June 2018 to July 2020, with approval of the CITM Ethics Committee. The study complied with the Helsinki Declaration and all study subjects signed the informed consent form before participating in the study. The case group included patients diagnosed with VTE according to the standard protocol[19]. There were 131 women and 131 men aged 18-95, median 58 years. Patient blood samples were collected at the Sestre milosrdnice University Hospital Center, Dubrava University Hospital and Merkur University Hospital from Zagreb. The control group of unrelated voluntary blood donors with no personal or family history of thromboembolic episodes included 48 women and 53 men aged 23-65, median 41 years.

Blood donor samples were collected at CITM. Peripheral blood was sampled in a Vacutainer K_2EDTA tube, 8.5 mL (Becton Dickinson, UK). Genomic DNA

was isolated from 200 μL whole blood on a QIAcube device using a QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Germany), with elution volume of 200 μL. The reagents used for genotyping MTHFR mutations were CustomTaqMan SNP Genotyping Assay, MTHFR C677T-SNP assay C_1202883_20, Chr 1 (rs 1801133), MTHFR A1298C-SNP assay C_850486_20, Chr 1 (rs 1801131) (Applied Biosystems, USA). Genotyping was performed on an ABI Prism 7500 real-time PCR system (Applied Biosystems, USA). The reaction mix volume was 25 μL and the RT-PCR amplification program was as follows: 50 °C 2 min; 95 °C 2 min; 40 cycles (95 °C 15 sec; 60 °C 1 min); 60 °C detection of fluorescence.

The χ^2-test, odds ratio (OR) with 95% confidence interval (95% CI) and comparison of proportions were used to determine statistical significance of differences in the distribution of MTHFR C677T and A1298C genotypes and alleles between the patient and control groups. All p values below 0.05 were considered significant. The relationship between MTHFR genotype frequencies in the populations was analyzed using the Hardy-Weinberg equilibrium test. Statistical analyses were performed using MedCalc, version 19.5.3 (Belgium) software.

Results

Distribution of genotypes in the control group showed no significant deviation from Hardy-Weinberg equilibrium (p=0.924 for C677T and p=0.960 for A1298C), which indicated a statistically worthy comparison with the patient group. There was no statistically significant difference in the distribution of MTHFR genotypes between the patient and control groups either in C677T mutation (p=0.676) or A1298C mutation (p=0.872).

Distribution of mutated alleles did not show any significant differences either (C677T p=0.808 and A1298C p=0.738) (Table 1). We analyzed difference in the genotype and allele frequencies of the MTHFR mutations according to genders (Table 2). There was no statistically significant difference in the frequencies of genotypes and alleles between women and men in the VTE and control group. The greatest difference of 6.6%, which was not statistically significant (p=0.245), was observed in the group of men carriers of TT genotype for C677T mutation between the diseased and healthy ones (Table 2).

Additionally, we examined thrombotic risk in carriers of the possible combinations of C677T and A1298C MTHFR genotypes (Table 3). The highest

Table 1. Genotype and allele frequencies of MTHFR mutations C677T and A1298C

MTHFR mutation	**Cases N=262 (%)**	**Controls N=101 (%)**	χ^2	**p**	**OR (95% CI)**
C677T					
CC	117 (44.6)	44 (43.6)	0.782	0.676	1.297 (0.649-2.592)
CT	106 (40.5)	45 (44.5)			
TT	39 (14.9)	12 (11.9)			
Allele C	340 (64.9)	133 (65.8)	0.059	0.808	1.043 (0.741-1.468)
Allele T	184 (35.1)	69 (34.2)			
A1298C					
AA	124 (47.3)	45 (44.6)	0.272	0.872	0.894 (0.564-1.419)
AC	109 (41.6)	45 (44.6)			
CC	29 (11.1)	11 (10.8)			
Allele A	357 (68.1)	135 (66.8)	0.112	0.738	0.943 (0.667-1.332)
Allele C	167 (31.9)	67 (33.2)			

MTHFR = methylenetetrahydrofolate reductase; OR = odds ratio; CI = confidence interval; p = probability

Table 2. Comparison of MTHFR genotypes and allele frequencies between genders

Mutation	Genotype	Women				Men			
		Cases N=131 (%)	Controls N=48 (%)	Difference %	p (95% CI)	Cases N=131 (%)	Controls N=53 (%)	Difference %	p (95% CI)
C677T	CC	56 (42.7)	19 (39.6)	3.1	0.710	61 (46.6)	25 (47.2)	0.6	0.941
	CT	57 (43.5)	22 (45.8)	2.3	0.784	49 (37.4)	23 (43.4)	6.0	0.451
	TT	18 (13.8)	7 (14.6)	0.9	0.878	21 (16.0)	5 (9.4)	6.6	0.245
A1298C	AA	62 (47.3)	23 (47.9)	0.6	0.943	62 (47.3)	22 (41.5)	5.8	0.476
	AC	56 (42.7)	21 (43.8)	1.1	0.896	53 (40.5)	24 (45.3)	4.8	0.551
	CC	13 (9.9)	4 (8.3)	1.6	0.747	16 (12.2)	7 (13.2)	1.0	0.853
	Allele								
C677T	T	75 (57.3)	29 (60.4)	3.1	0.710	70 (53.4)	28 (52.8)	0.6	0.941
A1298C	C	69 (52.7)	25 (52.1)	0.6	0.943	69 (52.7)	31 (58.5)	5.8	0.476

p = probability; CI = confidence interval

Table 3. Frequency of combined MTHFR C677T and A1298C mutations

Combination		Controls N=262 (%)	Cases N=101 (%)	Difference (%)
C677T	A1298T			
CC	AA	33 (12.6)	11 (10.9)	1.7
CC	AC	55 (21.0)	22 (21.8)	0.8
CC	CC	29 (11.1)	11 (10.9)	0.2
CT	AA	53 (20.2)	22 (21.8)	1.6
CT	AC	53 (20.2)	23 (22.8)	2.6
CT	CC	0 (0.0)	0 (0.0)	0.0
TT	AA	38 (14.5)	12 (11.8)	2.6
TT	AC	1 (0.4)	0 (0.0)	0.4
TT	CC	0 (0.0)	0 (0.0)	0.0

prevalence in both study groups was a combination of heterozygous carriers for both mutations, CT/AC, as expected, which does not reflect any risk. Although the greatest difference in the prevalence was found for the combination of TT/AA genotypes (2.6%), it was not statistically significant (Table 3).

Discussion

Ten years earlier, Jukić *et al.* conducted a retrospective case-control study in the Croatian population to examine the effect of ABO blood group genotypes, factor V Leiden (FVL), prothrombin G20210A and MTHFR C677T on the development of thrombosis. Isolated MTHFR mutation was found not to be a prothrombotic risk factor in the examined group of patients, unlike the non-O blood group which was found to carry a 2-fold higher thrombotic risk[20]. The results of our research agree with the results of this previous study even after the introduction of the second MTHFR A1298C mutation. We did not observe a significant difference in genotype and allele frequencies, for both mutations separately or combined. Like our study, a Polish case-control study on 149 VTE cases and 100 controls confirmed FVL and prothrombin G20210A

as risk factors, in contrast to MTHFR mutation[14]. A study involving 250 samples *per* group of VTE patients and controls from India (Kashmir) did not find a statistically significant association of the MTHFR C677T mutation with the VTE risk[18].

The relevance of common MTHFR mutation as an independent risk factor greatly differs for distinct populations and remains contradictory. It should be emphasized that the distribution of MTHFR mutations varies and depends on the ethnic origin of the studied populations, which contributes to the heterogeneity of results. Contrary to our population, for the Turkish population, Basol *et al.* found that T allele frequency of C677T MTHFR was significantly higher in patients than in controls. They also found that association of combined wild genotypes, CC homozygotes (C677T locus) and AA homozygotes (A1298C locus), contributes to a lower risk of developing PE[21]. Hosseini *et al.* conducted a retrospective case-control study on the Iranian population and found a significant association of DVT and C677T and A1298C mutations (OR 6.0 and 8.3, respectively)[12]. The case-control study of 212 Mexican VTE patients found the T allele of C677T mutation to be significantly more prevalent among VTE patients and the tendency of TT carriers to have elevated hyperhomocysteinemia[22].

In the assessment of risk factors for multifactorial diseases, the most informative is meta-analysis. The most recent meta-analysis by Gao *et al.* included 15 studies with participants of Asian descent and 12 studies of Caucasian populations. They conclude that the C677T MTHFR polymorphism may increase susceptibility to VTE in Asians, but not in Caucasians. However, no association between the A1298C polymorphism and VTE was found, regardless of the subject race[23]. Similar results arise from a meta-study in 2013 by Simone *et al.*, which included 37 studies on VTE risk, mostly from European databases, on 11,239 cases and 21,521 controls. MTHFR C677T mutation showed no association with thrombotic risk, either single or combined with FVL or prothrombin 20210A[23]. Recently, Zeng *et al.* conducted a meta-analysis of 99 studies to examine the effects of the C677T and A1298C mutations on VTE risk. They conclude that the A1298C mutation significantly correlates with the PE risk, whereas the C677T mutation has been proposed as a predictive marker for the development of DVT and PE in Caucasians, East and West Asians[25].

The outcome of each study should be evaluated concerning limitations that may lead to false conclusions. Unlike exclusively hereditary factors such as FVL and prothrombin G20210A, estimation of thrombotic risk of the so-called mixed factors such as MTHFR mutations depends on additional factors, e.g., vitamin supply, metabolic products, etc.[17]. In this study, we could not evaluate the combined effect of both mutations on VTE risk because there were no homozygous carriers of mutated alleles for C677T and A1298C due to already observed relatively low frequency of homozygous genotype of A1298C mutation (10.6%) and highly significant linkage disequilibrium between MTHFR C677T and MTHFR A1298C polymorphisms found in the Croatian population[26]. Another limitation of the study was that neither Hcy concentration nor vitamin B levels were measured in study participants.

Inclusive, the results of this study do not support the hypothesis that MTHFR mutations C677T and A1298C represent an independent risk factor for the development of VTE. There was no statistically significant difference in the distribution of MTHFR genotypes and alleles between the patient and control groups either in C677T mutation or in A1298C mutation.

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Sažetak

PROCJENA TROMBOTIČKOG RIZIKA MUTACIJA C677T I A1298C GENA ZA METILENTETRAHIDROFOLAT REDUKTAZU ZA RAZVOJ VENSKE TROMBOEMBOLIJE

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MTHFR mutacije C677T i A1298C uz nedostatak folata i vitamina B12 dovode do hiperkoagulabilnosti. U radu smo procjenjivali povezanost MTHFR mutacija s trombotičkim rizikom kod bolesnika s venskom tromboembolijom (VTE), pojedinačno i u kombinaciji. Istraživanje parova obuhvatilo je skupine od 262 bolesnika s VTE i 101 zdravog ispitanika. Razdioba alela MTHFR C677T/A1298C određena je pomoću lančane reakcije polimerazom u stvarnom vremenu, a rezultati su statistički analizirani pomoću χ^2-testa i usporedbom proporcija s 95% intervalima pouzdanosti (95% CI) i p=0,05. Nije bilo statistički značajne razlike u učestalosti genotipova MTHFR C677T između skupine bolesnika i kontrolnih osoba (p=0,676; OR=1,297; 95% CI 0,649-2,592), kao ni za mutaciju A1298C (p=0,872; OR=0,894; 95% CI 0,564-1,419). Razdioba alela obiju mutacija MTHFR nije pokazala značajne razlike: C677T p=0,808; OR=1,043; 95% CI 0,741-1,468 i A1298C p=0,738; OR=0,943; 95% CI 0,667-1,332. Razdioba genotipova MTHFR analizirana χ^2-testom među spolovima nije pokazala značajnu razliku. Pri evaluaciji kombinacije mutacija najveća razlika između slučajeva i kontrolnih osoba pronađena je u frekvencijama nositelja MTHFR TT/AA (2,6%), što također nije značajno (p=0,520). Može se zaključiti da mutacije MTHFR C677T i A1298C ne predstavljaju čimbenike rizika za razvoj VTE u skupini bolesnika iz Hrvatske.

Ključne riječi: *MTHFR (metilentetrahidrofolat reduktaza); Venska tromboembolija; Genotip; Aleli*